

(o) applying said active eluates on Sephadex G200 column and eluting with phosphate buffer containing 0.1M of NaCl.

27. The preparation method, as recited in claim 26, after the step (o), further comprising the steps of:

- (p) pouring protein peaks;
- (q) estimating an antibody activity with "ELISA"; and
- (r) sterilizing by 0.22 $\mu$  membrane filtration and lyophilizing to achieve a purified IgY against dental caries bacteria.

#### REMARKS-General

1. Upon review of the original specification and in light of the observation of the Examiner noted in the above Office Action, the applicant has submitted a completely revised substitute specification which is deemed to more clearly and distinctly describe the subject matter of the instant invention, and which provides full antecedent basis to the newly drafted claims. No new matter has been included in the substitute specification.

2. A marked-up copy is also submitted to show additions to and/or deletions from the original specification and the substitute specification includes the same changes as are indicated in the marked-up copy of the original specification showing addition and/or deletions.

3. The newly drafted independent claim 13 incorporates all structural limitations of the original claim 1 and includes further limitations previously brought forth in the disclosure. No new matter has been included. All new claims 13 to 27 are submitted to be of sufficient clarity and detail to enable a person of average skill in the art to make and use the instant invention, so as to be pursuant to 35 USC 112.

**Response to Rejection of Claims 1 to 7 under 35USC112**

4. The applicant submits that the newly drafted claims 13 to 27 particularly point out and distinctly claim the subject matter of the instant invention, as pursuant to 35USC112.

**Response to Rejection of Claims 1 to 7 under 35USC103**

5. The Examiner rejected claims 1 to 7 over Lee et al. and/or Akita et al. in view of Hatta et al. or Hamada et al. or Natarajan et al., but these patents fail to suggest the invention of newly drafted claims 13 to 27.

6. The cited art, Lee et al., suggests a LARGE-SCALE PURIFICATION OF EGG IMMUNOGLOBULIN that emphasizes on purification of IgY with a more complicated reparation procedure. It contains several times of ion exchange and process of precipitation or gel filtration and de-salting. Accordingly, the cited art, Lee et al, substantially differs to the instant invention in many aspects as follows:

(i) The instant invention involves with the whole preparation process, which also comprise the steps of preparing streptococcus mutans antigens and immunizing hens. Moreover, the procedure is simple and low cost. Purification of IgY in the present invention only contains applying DEAE-Sephadex A50 and Sephadex G200 once. Since these two materials are both recyclable, cost of preparation will drop down.

(ii) In the extracting of crude IgY, *Lee et al.* Add 1% caprylic acid in the diluted yolk when homogenize the yolk. Therefore, it increases the likelihood of chemical pollution. In the instant invention, DEAE-Sephadex A50 and Sephadex G200 are both inert substances and no materials used in the instant invention would cause chemical pollution.

(iii) Although both the Lee et al. and the instant invention comprise step of gel filtration, the used materials are different. In *Lee et al.*, bound antibody fraction was diluted and chromatographed on a column of ACA44. In the instant invention, this gel filtration step can function as molecular sift. The high molecular weight proteins are eluted first and various proteins are then eluted according to molecular size in decreasing order. The separate limit of Sephadex G200 is 5000-800000 Dalton.

7. The cited art, Hatta *et al.*, on the other hand, teaches a method preparation against dental carries using Streptococcus mutants serotype c, but Hatta et al didn't mention serotype d and their best ratio. Using mention serotype c and d and finding their best ratio are innovative points of the claimed invention. By the way, we have to point out that the content of Hatta et al research is unrelated to its coversheet that it doesn't refer to the real content of Hatta's research.

8. The cited art, Hamada *et al.*, merely suggests how to isolate Streptococcus mutants from children and implant them in rats. Furthermore, Hamada et al. mentioned serotypes c, d, e and f induced dental caries in SD rat. But it is different from the instant invention in view of purpose, principle and content, so there is no comparability between them.

9. The cited art, Natarjan *et al.*, teaches the method of preparing immunoglobulins from lizard serum. It doesn't belong to the same topic of preparing IgY because these two are different immunoglobulin. It simply suggests how to obtain immunoglobulin from lizard serum and its mole weight is 85,500D, and the latter is from yolk of eggs and its mole weight is 180,000D.

10. The applicant respectfully submits that the invention must be considered as a whole and there must be something in the reference that suggests the combination or the modification. See Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984) ("The claimed invention must be considered as a whole, and the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination"), In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984), ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989), ("Although the Commissioner suggests that [the structure in the primary prior art reference] could readily be modified to form the [claimed] structure, "[t]he mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.")

11. In the present case, there is no such suggestion. In any case, even combining Lee et al., Akita et al., Hatta et al., Hamada et al., and Natarajan et al. would not provide

the invention as claimed -- a clear indicia of nonobviousness. Ex parte Schwartz, slip op. p.5 (BPA&I Appeal No. 92-2629 October 28, 1992), ("Even if we were to agree with the examiner that it would have been obvious to combine the reference teachings in the manner proposed, the resulting package still would not comprise zipper closure material that terminates short of the end of the one edge of the product containing area, as now claimed."). That is, modifying Lee et al. and/or Akita et al. with Hatta et al. or Hamada et al. or Natarajan et al., as proposed by the Examiner, would not provide the following features:

(a) A long period of validity: In the claimed invention, after immunization hens, eggs can keep active antibody (immunoglobulin of yolk) for approximately 13 months. In current documents, this duration of existing techniques is only half a year. So, the period of validity increases two times than the current techniques.

(b) High titer of antibody: If existing preparative techniques are used to prepare antibody, the highest titer is only 1:320 at present. In the instant invention, the titer can be 1: 512. And the ELISA estimating antibody activity and be 204800. More antibodies can be produced in the instant invention in the same circumstance.

(c) Good effect on restraining activity of streptococcus mutans: Research has showed that forty eight hours after different concentrations of IgY are put into culture medium of streptococcus mutans, activity of streptococcus mutans is restrained, and the pHs raises to different extents. This result proves that every pH is above 6.0 (Experiment proves dental caries occur only at the critical value pH 5.0~5.5 or even below). Therefore, IgY can effectively protect people's teeth.

(d) No chemical pollution and comprehensively utility of remains: There is no chemical pollution in the preparation process. The eggshell, egg white and the remainder of yolk after extracted can be utilized comprehensively. Eggshell can be used to make calcium powder; egg white can be made into peptone or food; remained yolk can be utilized as lecithin, vitelline oil and other food. There leaves no cast off, therefore there is no environmental pollution.

(e) Low preparation cost: In both processes of extracting crude IgY and purifying extracted IgY, the techniques are very simple and DEAE-Sephadex A50 and

Sephadex G 200 can be utilized repeatedly. Therefore, the whole preparation cost is relatively lower than current techniques.

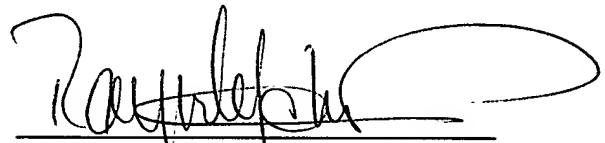
(f) Implementation probability: The success ratio of implementing the instant invention will reach 100% if the implementation strictly follows the operation of the instant invention.

#### **The Cited but Non-Applied References**

12. The cited but not relied upon references have been studied and are greatly appreciated, but are deemed to be less relevant than the relied upon references.

13. In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the objection and rejection are requested. Allowance of claims 13 to 27 at an early date is solicited.

Respectfully submitted,

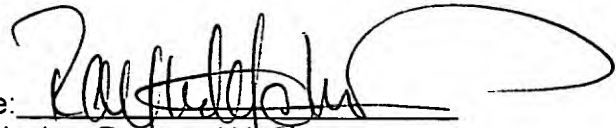


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